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Cognitive-behavioural therapy for adult attention deficit hyperactivity disorder: a proof of concept randomized controlled trial

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Abstract

Objective

To investigate efficacy, patient acceptability and feasibility of formulation-based cognitive behavioural therapy (CBT) for adults with attention deficit hyperactivity disorder (ADHD). NICE guidelines for adult ADHD recommend further research into psychological treatments.

Method

60 participants with adult ADHD were randomly allocated to treatment as usual (TAU) vs TAU plus up to 16 sessions of individual formulation-based CBT for ADHD.

Results

Adding formulation based CBT to TAU for ADHD significantly improved ADHD symptoms on the Barkley Current Symptoms Scale and scores on the Work and Social Adjustment Scale. Adjusted effect sizes (ES) were 1.31 and 0.82 respectively.

There were also significant improvements on secondary outcomes including independently evaluated clinical global improvement, self-rated anxiety, depression, global distress and patient satisfaction (adjusted effect sizes 0.52-1.01).

Conclusions

This is the first randomized controlled trial to provide preliminary evidence of efficacy and acceptability of individual formulation-based CBT for ADHD when added to TAU over TAU alone. This approach now needs to be tested in a larger multi-centred randomized controlled trial.

Keywords: randomized controlled trial, adult, attention deficit disorder with hyperactivity, cognitive therapy

Running head: cognitive behavioural therapy for adult ADHD

Significant Outcomes

This is the first clinical trial to provide evidence of the effectiveness of individually delivered formulation-based cognitive-behavioural therapy for adult ADHD.

When added to treatment as usual, cognitive behavioural therapy had significantly greater success in both reducing ADHD symptoms and improving occupational and social functioning than treatment as usual alone.

Limitations

A high number of participants in the TAU group were lost to follow-up. However the sensitivity analysis suggests that even when taking this into consideration, the treatment effect was robust.

The study design does not control for therapist time and attention.

We excluded participants with an alternative primary diagnosis or severe co-morbidities which could affect the generalisability of the findings. This was because we wanted the CBT to focus on ADHD and associated problems as opposed to a separate primary clinical problem. However individualised formulation can be complex so it seems likely this approach, which has been shown to be effective in reducing emotional distress, could be adapted for people with ADHD who have severe co-morbidities.

Introduction

While medication remains the first line of treatment for attention deficit hyperactivity disorder (ADHD) in adults, National Institute for Health and Care Excellence (NICE) guidelines for the condition (1) recommend that medication be complemented by cognitive behaviour therapy (CBT) and that further research focus on developing psychological treatments. Most studies have investigated group treatments, and indeed on the basis of current evidence NICE recommends these as they are most cost-effective. However ADHD presentations tend to vary widely and, even though many of the group approaches use individual coaches/support persons to help participants apply the skills to their own difficulties, group treatments provide less flexibility than individualised therapies to address idiosyncratic difficulties. Indeed a recent study found that a highly structured group intervention specifically developed to address ADHD-related difficulties did not outperform individual non-specific counselling and this may have been one of the reasons (2).

There have been four randomized controlled trials of individualised CBT that are structured and manualised (3-6). All found that CBT reduced ADHD symptoms (self and independently rated) compared with the control treatment(s). However in the Virta study whilst some encouraging improvements were seen in the CBT condition, most results were not statistically significant. Safren et al's studies used larger samples and longer interventions and moderate to large effect sizes were found on the primary outcomes. The Weiss et al study compared CBT plus placebo with CBT plus medication. Both groups showed statistically significant improvements in symptoms and functioning between baseline and the outcome points. The approaches in both the Safren and Weiss studies were similar in that they were modular and behavioural in nature and neither appeared to use 'Beckian' individualised case formulations to guide the treatment.

Uncontrolled studies have used individualised case formulations to tailor the CBT for ADHD (7, 8). These authors have described models derived from Beck's cognitive therapy (9) in which the core ADHD

symptoms contribute to the development of negative underlying beliefs (dysfunctional assumptions and core beliefs) and maladaptive coping strategies. While results are promising, there is as yet no randomized controlled trial evaluating this approach. The advantage of individualised case formulation is that central themes binding apparently disparate problems or symptoms can be identified, enhancing clients' understanding (and hence engagement) and allowing techniques to be directly targeted. The formulation based approach has greater flexibility to focus specifically on the patient's key presenting difficulties. It can be both ADHD-specific and at the same time address associated emotional disorders which may have a reciprocal maintaining relationship with the ADHD symptoms. The primary aim of the current study was therefore to investigate efficacy, patient acceptability and feasibility of a formulation-based cognitive behavioural therapy for adults with ADHD (10). It was hypothesised that CBT plus treatment as usual would be more effective than TAU alone in i) reducing ADHD symptoms and ii) improving functioning at 42 weeks after the start of the study (12 weeks post-active CBT treatment).

Methods

This RCT was approved by the City Road and Hampstead Research Ethics Committee (reference 09/H0721/49) and registered as a controlled trial (ISRCTN 03732556). Participants were recruited from a specialist adult ADHD clinic between April 2010 and June 2013. They were included in the trial if they i) gave written informed consent ii) were 18-65 years of age, iii) had been diagnosed with adult ADHD (with childhood onset) by a mental health professional, iv) scored 6 or more on either the inattentive or the hyperactive/impulsive subscale of the Adult Barkley Current Symptoms Scale (self-rated) (11) and v) were rated to have at least moderate clinical severity as indicated by a score of 4 or more on the Clinical Global Impression scale (12).

Participants were excluded if i) ADHD was not the dominant clinical diagnosis, i.e. they had a clinically significant anxiety disorder and/or current episode of major depression, significant risk of self-harm, active substance misuse/dependence in the last three months, an acquired brain injury, primary diagnosis of psychosis or bipolar disorder, a pervasive developmental disorder, a previous diagnosis of a personality disorder or any other dominant clinical diagnosis whereby participation in the trial would be inappropriate for their clinical needs and/or where treatment of the primary disorder was warranted; ii) they had a verbal IQ of less than 80; iii) they were unable to meet the requirements of an RCT (e.g. not able to attend regularly and reliably for sessions); iv) they were currently undergoing another talking therapy for ADHD or any other psychiatric disorder; v) they were unable to speak English at an adequate level to participate; vi) if on medication, they were stabilised on the medication type and dose for less than three months. However the latter criterion was removed several months into the trial with the agreement of the Trial Steering Committee (TSC) in a bid to improve recruitment rates. The TSC advised that the randomized controlled design would control for any differences in medication between the two groups.

Diagnosis of adult ADHD was confirmed using adult symptoms in the Conners' Adult ADHD Diagnostic Interview for DSM IV (CAADID) (13). Presence of other co-morbid conditions was assessed using the Mini-International Neuropsychiatric Interview (MINI) (14).

Interventions

For brevity, the two treatments will be referred to as CBT and TAU rather than CBT plus TAU and TAU alone.

Treatment as usual

All participants in the trial received TAU. This included visits to their clinic doctor in the service, if applicable, or visits to their local specialist ADHD service, community mental health team (CMHT) or general practitioner (GP) for management of their ADHD. All TAU sessions focused on medication management and related issues such as side-effects. It was verified at research visits that participants were not given information or advice with regard to psychosocial strategies to manage their ADHD symptoms. There was no additional therapist involvement.

CBT

In addition to TAU, participants randomized to CBT attended up to 15 CBT sessions over 30 weeks. They had a sixteenth, follow-up, CBT session at 42 weeks (just prior to the main outcome point). A CBT manual was developed and updated iteratively. Treatment was divided into four stages.

During stage 1 (engagement and treatment planning; sessions 1-3), information was given about adult ADHD and a shared formulation derived. The formulation made links between the individual's predisposition (i.e. vulnerability factors such as genetic make-up and personality), early life experiences and current coping behaviours and cognitions. Goals for treatment were agreed.

Stage 2 (active treatment; sessions 4-13), involved working towards the goals, in particular focusing on the problematic cognitions and behaviours identified in the assessment and initial formulation. Earlier sessions focused on problem-solving and adaptive skills such as time management and organisation,

where indicated by the goals and formulation. Cognitive techniques such as thought challenging and behavioural experiments were used to question and test unhelpful beliefs. Guidance was provided on managing impulsivity and unhelpful emotional responses. A detailed longitudinal formulation was developed identifying key core beliefs, rules for living, unhelpful compensatory strategies and their effects. Explicit links were made between these and ADHD-related difficulties. For example, a participant held beliefs about not being good enough as they had been criticised throughout their life for being disorganised. They had coped by avoiding responsibilities which compounded their underlying beliefs. A new formulation with new core beliefs, rules for living and helpful coping behaviours was then derived. Participants found evidence for their new beliefs by experimenting with the new coping behaviours.

In stage 3 (preparation for the future; sessions 14 and 15), participants completed a 'blueprint for therapy', recording what they had learned and how to continue to implement these changes in the future. Goals for treatment were re-rated.

Stage 4 (follow-up; session 16), took place just prior to 42 weeks from baseline. Participant and therapist reviewed any change since the end of active treatment, re-rated goals, identified any further gains made and discussed management of any setbacks.

Throughout, treatment was adapted for ADHD with emphasis on agenda setting, staying on-task during sessions, rehearsal of adaptive coping skills, problem-solving any ADHD-related therapy interfering behaviour (such as non-completion of homework, arriving late or forgetting sessions) and revisiting the individual's history in linking current beliefs and behaviour with early life experiences.

The treating therapists were a clinical psychologist and a counselling psychologist who both had experience in treating ADHD in adults. One psychologist (MS) treated 5 of the CBT cases whilst the other (AD) treated 25. A senior CBT therapist provided joint supervision.

A number of common themes emerged which were very similar to those previously described by other authors (15). Schema included self-mistrust, failure, incompetence, inadequacy and instability (e.g I am

irresponsible/unreliable, I am not good enough, I am ineffective, I am inferior to others/worthless, I am out of control). These appeared to be related to the individual's experiences such as criticism from significant others, experiencing cognitive difficulties in comparison with peers, traumatic childhood experiences (such as neglect or abuse) and 'over-protective' parenting. Similar common compensatory strategies to those previously described were also observed including anticipatory avoidance/procrastination, brinksmanship, juggling, pseudoefficiency and stoicism. In addition, the following were also seen: withdrawal, ignoring/suppressing own needs and emotions, verbal intimidation/aggression, perfectionism/setting unrealistic goals and rumination.

Commented [KCL1]: Was this towards others

Outcome measures

The assessments described below were administered at three time points: baseline (pre-treatment), 30 weeks (post treatment for the CBT condition) and 42 weeks (12 week follow-up for the CBT condition). The main outcome was at 42 weeks assessment. All assessments were carried out by an assistant psychologist. In addition, at weeks 30 and 42, an independent assessor (mental health professional in the same NHS trust), blind to treatment group, interviewed the participants and rated their clinical improvement and current functioning.

In order to address the validity of the blinding procedure, blind assessors were asked to complete a questionnaire at each assessment point noting the treatment group that they thought the participant was in and if this was (a) a guess, (b) revealed by the participant, or (c) due to another reason (which they were asked to state). Of the treatment completers, blind assessors were accurate in their assignment of treatment group in 21 (78%) of cases. Two (7%) participants 'unblinded' the assessor to treatment group (i.e., the assessor cited (b) as the reason for their choice of treatment group) and the blind assessor's described their choice as a 'guess' in 24 (89%) of cases. In one (4%) of the cases, the assessor cited (c) as the reason for group assignment stating that the participant had referred to the fact that being in the trial had 'helped him cope with his difficult personal circumstances'.

Primary outcome measures

Two primary outcomes were included. The first, the Adult Barkley Current Symptoms Scale (CSS) (11) includes questions assessing the frequency of the 18 DSM-IV ADHD symptoms; 9 inattentive and 9 hyperactive/impulsive symptoms on a scale ranging from 0 = “never or rarely” to 3 = “often”, with a score of 2 or above indicating presence of a symptom. A total score (maximum 54 points) is derived by summing all items in both categories, alternatively a subscale can be derived for the two constructs. We chose to use the total ADHD score. This measure has strong reliability and validity and has been widely used in ADHD research. Norms are available for clinically significant thresholds (16).

The other primary outcome was the Work and Social Adjustment Scale (WSAS) (17) which measures impairment in functioning in relation to a specific problem, in this case the participant’s ADHD symptoms. It consists of 5 questions each rated on an 8-point scale (0 = “not at all impaired” and 8 = “very severely impaired”). Reliability and validity of this scale has not been specifically investigated in adult ADHD. However studies in other conditions (depression and OCD) suggest that a score of 20 or more indicates moderately severe or worse psychopathology. Scores of 10 to 20 are associated with significant functional impairment but less severe clinical symptomatology and scores below 10 are associated with subclinical populations.

Secondary outcome measures

Self-report measures included the Hospital Anxiety and Depression Scale (HADS) (18), the Clinical Outcomes in Routine Evaluation Outcome measure (CORE-OM) (19), the Clinical Global Impression scales, Improvement and Satisfaction versions (CGI) (12, 20). CGI scales were recoded as binary variables from their original 5 point scale. CGI improvement was coded as improved if participants felt “very much better” or “much better” and not improved otherwise. Participants were coded as satisfied if they responded “very satisfied” or “moderately satisfied” and not satisfied otherwise. The independent (blind) assessor was also asked to complete the CGI Improvement scale which was recoded as binary in the same way as the self-report scale. The evaluator based their CGI ratings on a semi-structured interview that was

devised by the research team asking a number of open-ended questions about the participant's symptoms and functioning, included in the supplementary information. Finally an informant – a person who knew the participant well such as parent or spouse – was asked to complete the informant version of the CSS (11).

Randomisation

Participants were randomized to one of the two groups using sequence generated randomisation tables and fixed length blocks (length concealed), stratified for gender. Randomisation was performed by an independent group in another service in the same NHS trust using a concealed sequence. The independent statistician and the independent assessor who assessed the participants at weeks 30 and 42 were both blind to the treatment allocations.

Treatment fidelity

All CBT cases were recorded to assess treatment fidelity. A proportion (25%; 8 recordings) of cases of session 4 were randomly selected and rated by two independent therapists outside of the clinical trial as to overall therapeutic alliance and the extent to which the therapist adhered to the manual (7-point Likert scales). The raters co-rated 50% of the recordings to establish inter-rater reliability. Therapists' adherence to the manual and therapeutic alliance median scores were high (both 6/7).

Statistical methods

Sample Size

The sample size calculation was based on a previous study by Safren et al (2005) which compared CBT plus continued medication with continued medication only. This study found the change score of the mean was 9. A sample size of 23 in each group would be needed to have 90% power to detect a difference of

this size with an α level of 0.05. To account for dropout, recruitment was aimed at 30 participants per group.

Statistical analysis plan

Prior to analysis, a statistical analysis plan was agreed with the Trial Steering Committee (TSC). Analysis was intention to treat and linear mixed effect models were used to analyse the primary outcomes, mean group differences for CSS and WSAS at 42 weeks. Both 30 and 42 week scores were included in the analysis model, with an interaction between treatment and time to allow treatment estimates to differ at 30 to 42 weeks. Outcomes were adjusted for baseline outcomes scores and age as fixed effects. To account for correlations between repeated measures within participants, analysis models included a random intercept.

Before the analysis plan was finalised, secondary outcome measures were selected. Secondary outcomes at 42 weeks were fit using similar models where these outcomes were continuous. It was intended to use mixed effects logistic regression for the binary clinical global improvement and satisfaction outcomes. However, the small number of events in the control group meant that treatment estimates were unstable and thus Fisher's exact test was used instead. Group differences in adverse events were compared with Fisher's exact test, both by person and event as 3 people had more than 1 adverse event.

The following procedures were used to deal with missing data. Where 75% or more questions were answered on a single questionnaire, missing answers were imputed with the mean of remaining answers on that questionnaire for that participant. Otherwise that particular questionnaire outcome for that participant was treated as missing. Two approaches were used to deal with missing outcome data. Firstly, the main analysis used mixed effects models fit using maximum likelihood (ML). These models allow all available data to be included in the analysis, under the assumption that data is missing at random (MAR), that is predictors of baseline missingness being included in the model. No baseline predictors of missingness were found (using logistic regression and Fisher's exact test). In addition, the MAR assumption was explored in a sensitivity analysis in which values of missing primary outcome scores were imputed

which would change the clinical interpretation of the effect (21). The degrees of freedom for statistical tests and confidence intervals were derived using the Kenward-Rogers approximation. Both adjusted and unadjusted mean treatment effects were reported, with 95% confidence intervals and significance levels for adjusted treatment effects and effect size (Hedges g) for unadjusted effects. All analyses were done in R v 3.0.3 with the packages lme4 and pbKRtest.

Results

Participant Flow

Figure 1 about here

Figure 1 shows participant flow from screening to follow-up. The main reasons for not participating were not meeting the study criteria ($n=929$) and declining to participate ($n=139$). The reasons for not meeting the study criteria were: outside the age limit ($n=9$), not diagnosed with adult ADHD ($n=83$), CSS or CGI score too low ($n=88$), ADHD not the primary diagnosis ($n=596$), verbal IQ of less than 80 ($n=32$), unable to meet the requirements of an RCT ($n=63$), currently undergoing or on the waiting list for another talking

therapy (n=45), not stabilised on medication (n=13; with agreement from the TSC this criterion was removed a few months into the trial, to maximise recruitment).

60 people who met study criteria and gave written informed consent were randomized to either TAU (n=30) or CBT (n=30).

In the TAU group one participant did not receive the allocated intervention deciding to take up routine (non-trial) CBT sessions in the service. However the participant remained in the trial for the research assessment follow-up. Two people in the TAU group discontinued the intervention and withdrew from the trial: one because they were unhappy at being allocated to TAU and another had a change in personal circumstances. A further nine were lost to follow-up. In the CBT group, two people discontinued the intervention: one did not think CBT was needed and another discontinued due to a change in personal circumstances. A further one was lost to follow-up. There was a significantly higher loss to follow-up for TAU (13 for primary outcome) than CBT (3 for primary outcome). A full presentation follows below in the missing data section.

People in the CBT group attended a mean of 1.2 (SD 2.0) ADHD medical appointments over the period of the trial while people in the TAU group attended a mean of 1.8 (SD 2.9). There was no significant difference between the two groups. Almost all trial completers in the CBT group attended all 16 CBT sessions offered, only two trial completers missed sessions; one participant missed three sessions and one missed two. (Due to potential erratic attendance, therapists were flexible in rescheduling CBT appointments so that all 16 sessions could be attended wherever possible in the necessary timescale).

Participant characteristics and baseline medication

The 60 participants were well balanced on age, ethnicity, education and marital status (see table 1). There were 7 more men in the CBT group than TAU but the authors are not aware of any evidence to suggest that there are gender differences in response to CBT treatment. Clinically at baseline the two groups were very similar in terms of ADHD symptoms (CAADID and CSS). They were also similar in terms of medication

use: 24 participants in the CBT group were stable with regard to medication status (either not taking it at all or on the same medication type and dose) for three months or more at baseline, versus 22 in the TAU group. In terms of ADHD medication, 19 participants in the CBT group were on ADHD medication versus 26 in the TAU group; in terms of other psychotropic medication, 8 participants in the TAU group were on SSRIs versus 2 in the CBT group. One participant in the CBT group was taking a benzodiazepine (see Table 2). Both groups were also similar in terms of anxiety and depression scores. Taking 11 as the threshold on each subscale on the HADS, 14 were in the moderate to severe anxiety range in each group. One person in the CBT group vs 4 people randomized to TAU were in the moderate to severe depression range.

Primary Outcomes

The results of the analysis are summarised in figures 2a and 2b table 3.

CSS: The CBT group showed a large improvement in both primary outcomes relative to the TAU group. At 42 weeks, the treatment difference for CSS scores was 8.8 points lower in the CBT group relative to TAU, (standardised ES = -1.31, $p < 0.001$). Checking the robustness of the results using Markov Chain Monte Carlo sampling, similar estimates were obtained with a treatment effect of 8.74 (95% Bayesian Credible Interval: 5.0 to 13.3). At 30 weeks the effect of treatment was marginally larger (ES: -1.52, $p < 0.001$)

WSAS: Similarly the WSAS scores were 6.6 points lower in the CBT group than TAU, (standardised ES = -0.82, $p = 0.003$). Similarly a MCMC model estimated the group difference as 6.44 points (95% BCI: 3.2 to 10.3). At 30 weeks the standardised ES was identical (ES = -0.82, $p = 0.002$)

Secondary Outcomes

CGI: Only small numbers of participants improved in the TAU group compared to the CBT group and thus the inferential statistics are not particularly informative but presented for completeness. The odds ratio (OR) for participant rated CGI Improvement for CBT vs TAU was 23.1 ($p < 0.001$). For CGI Satisfaction the

OR was 23.2 ($p < 0.001$). For blind assessors the OR was not computable as 0 participants were rated as improved in the TAU group.

CSS Informant: There was a moderate but non-significant benefit of CBT at 42 weeks (standardised ES = -0.38) and 30 weeks (ES = -0.42)

HADS: HADS anxiety scores were lower at 42 weeks (ES = -0.6, $p = 0.012$) and at 30 weeks (ES = -0.62, $p = 0.015$) for CBT vs TAU. Similarly, HADS depression scores were lower at both 42 weeks (ES = -0.66, $p = 0.002$) and 30 weeks (ES = -0.61, $p = 0.006$).

CORE: For CORE sub-domains, the CBT group improved across all domains relative to TAU at both 42 and 30 weeks, although only Problems and Wellbeing showed a statistically significant decrease. The decrease was moderate for Problems (42 weeks, ES = -0.59, $p = 0.025$ and 30 weeks, ES = -0.58, $p = 0.023$), and large for Wellbeing (42 weeks ES = -1.03, $p = 0.02$; 30 weeks ES = -1.01, $p = 0.02$). For CORE Functioning and Risk, effects were small, below 0.3 at both 30 and 42 weeks (see Table 3).

Safety data and changes in ADHD medication through the course of the trial

There were eight adverse events for five people in the CBT group and three events for three people in the TAU group. Neither of these differences was significant, either by person ($p = 0.99$) or by symptom ($p = 0.49$). Only two of the events, both of which were in the CBT group, were deemed to be serious, as they required unplanned hospital treatment and these were both rated as 'definitely unrelated' to the trial. Further details of the adverse events are provided as supplementary data.

CGI Improvement rated by participants showed little association with changes in ADHD medication for each group at 30 weeks or 42 weeks. For those who improved at 42 weeks, only one person in the TAU group and no one in the CBT group changed medication between baseline and 30 weeks. From 30 to 42 weeks, three improvers in the CBT group and one improver in the TAU group changed their medication. Of these, two in the CBT group changed the type of their medication, whilst one in each group decreased medication.

Missing data and sensitivity analysis

More people were lost to follow-up in the TAU arm relative to the CBT arm. For the primary outcomes three out of 30 outcomes were missing in the CBT group versus 13 out of 30 in the TAU group, (OR 0.15, Fisher's exact test, $p = 0.007$). The relative difference in drop-out between groups suggests that missingness is non-ignorable and so a sensitivity analysis was undertaken in which values were imputed for the missing observations for the CSS based on particular scenarios. We focused on changes to the point estimate of the treatment difference as adding observations will lead to smaller standard errors due to increased sample size, but included confidence intervals as an approximation to likely interval estimates. In the first scenario we assumed scores for all participants who dropped out returned to their baseline level. This had little impact on the treatment difference with the advantage for the CBT group 8.8 (95% CI: 4.8 to 12.8 points on the CSS). In the second scenario we explored non-ignorable missingness. As we were interested in the conditions which would lead to eliminating the treatment effect, this might involve drop-out in the CBT arm being associated with worse outcomes and those in the TAU arm with better outcomes. If we assume that dropouts in the TAU arm returned to baseline and CBT dropouts had the worst possible outcome (a maximum score of 54 on the CSS) the treatment difference was 7.3 (95% CI: 2.7 to 12.1). In the third scenario we assumed CBT dropouts returned to their baseline score and derived the improvement necessary in the TAU dropouts in order for the 95% confidence interval to include 0. An improvement of 12 points for the dropouts in the TAU group meant the 95% CI included 0, treatment difference at 3.49 (95% CI: 0.1 to -7.1) in favour of the CBT group. We infer that our results are robust given that these scenarios are quite implausible.

Figure 2. Estimated means and 95 % confidence intervals by treatment group and time point (0, 30 and 42 weeks) for the CSS and WSAS. Confidence intervals are derived from the primary analysis models, with outcomes by treatment group adjusted by time, time by treatment group interaction and adjusted for baseline score for the respective measures and gender.

Figures 2a and 2b about here

Table 1. Baseline demographics and clinical characteristics of participants randomized to CBT or TAU (n = 60).

	CBT	TAU
	(n = 30)	(n = 30)
Age, years at randomisation : mean (SD)	35.7 (9)	36.1 (10.4)
Gender, male: n (%)	23 (79.3)	18 (60)
Ethnicity: Non-White: n (%)	16 (53.3)	13 (43.3)
Level of education: n (%)		
GCSE	3 (10.3)	1 (3.3)
A Level	19 (65.5)	18 (60)
Further	7 (24.1)	11 (36.7)
Marital Status, cohabit: n (%)	9 (30)	12 (40)
CAADID ^a : mean (SD)		
Inattentive	8 (1)	8.1 (1.4)
Hyperactive/Impulsive	4.6 (2.5)	4.9 (2.3)
ADHD Medication: n (%)		

Yes	19 (63.3)	26 (86.7)
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ADHD Medication Type: n (%)

Methylphenidate	16 (53.3)	18 (60.0)
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Dexamphetamine	1 (3.3)	7 (23.3)
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Dexamphetamine &

Modafinil	1 (3.3)	0 (0.0)
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Atomoxetine	1 (3.3)	1 (3.3)
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Other Medication: n (%)

Yes	3 (10.0)	8 (26.7)
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Other Medication Type: n (%)

SSRI	2(6.7)	8 (26.7)
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Benzodiazepine	1 (3.3)	0 (0.0)
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a Conners' Adult ADHD Diagnostic Interview for DSM-IV™(13)

Table 2. Full descriptive statistics (mean, sd and n) for primary and secondary outcome measures at baseline, 30 weeks (end of treatment) and 42 weeks (12 weeks after the end of treatment) for TAU vs CBT groups.

Measure	Group	Baseline		30 weeks		42 weeks	
		n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
CSS	CBT	30	34.5 (7.5)	27	21.3 (10.6)	27	20.8 (8.8)
	TAU	30	33.5 (6.1)	19	32.6 (7.8)	17	29.1 (7.5)
WSAS	CBT	30	20.0 (8.2)	27	12.8 (8.5)	27	10.2 (6.9)
	TAU	30	21.8 (8.0)	19	19.2 (8.4)	18	16.8 (8.8)
CSS Informant	CBT	27	28.4 (9.3)	22	20.9 (11.2)	26	20.0 (10.6)
	TAU	26	28.3 (9.6)	17	29.2 (10.1)	20	24.0 (10.1)
HADS Anxiety	CBT	29	10.3 (3.5)	27	7.5 (3.5)	27	6.8 (3.6)
	TAU	30	9.5 (3.9)	19	10.4 (3.6)	19	9.7 (4.0)
HADS Depression	CBT	30	5.5 (3.0)	26	3.1 (2.3)	27	3.3 (3.6)
	TAU	30	6.3 (3.7)	19	6.4 (3.7)	19	5.8 (2.9)
CORE-OM Total	CBT	29	40.8 (16.0)	26	29.2 (16.5)	27	26.6 (17.6)
	TAU	29	43.2 (21.5)	19	44.6 (23.0)	19	40.3 (22.4)
CORE Problems	CBT	29	18.3 (7.5)	26	11.6 (7.3)	27	10.9 (7.3)
	TAU	29	18.1 (9.2)	19	18.5 (10.2)	19	16.7 (9.2)
CORE Functioning	CBT	29	15.7 (7.2)	26	13.0 (7.6)	27	11.5 (7.8)
	TAU	29	18.5 (8.8)	19	18.6 (9.6)	19	16.3 (9.1)
CORE Wellbeing	CBT	29	5.9 (2.9)	26	3.9 (3.0)	27	3.6 (3.1)
	TAU	29	5.7 (3.9)	19	6.4 (4.0)	19	6.3 (4.2)
CORE Risk	CBT	26	1.0 (1.7)	26	0.7 (1.7)	27	0.4 (1.5)
	TAU	19	1.0 (2.6)	19	1.1 (2.1)	19	0.9 (2.3)
CGI		Baseline		30 weeks		42 weeks	
				n	Improved n (%)	n	Improved n (%)
CGI Improvement (Participant)	CBT			25	18 (72%)	27	16 (59.3%)
	TAU			19	1 (5.3%)	18	1 (5.6%)
CGI Satisfaction (Participant)	CBT			25	23 (92%)	27	24 (89%)
	TAU			18	4 (22%)	17	4 (24%)
CGI Improvement (Blind Assessor)	CBT			28	15 (54%)	26	15 (57.7%)
	TAU			19	1 (5.3%)	19	0 (0%)

Abbreviations: CSS – Adult Barkley Current Symptoms Scale (Participant and Informant), WSAS – Work and Social Adjustment Scale, CGI – Clinical Global Impression: Yes / No - (Participant Improvement and

Satisfaction, Blind Assessor Improvement), HADS – Hospital Anxiety and Depression Subscale, CORE-OM - Clinical Outcomes in Routine Evaluation Outcome Measure

Table 3. Adjusted mean group differences (CBT versus TAU), test statistics and adjusted effect sizes for primary and secondary outcomes between baseline and both 30 weeks and 42 weeks (main outcome point).

	Adjusted Mean	Test statistic and p	Adjusted	Adjusted Mean	Test statistic and p	Adjusted
	Difference†	value	Effect	Difference†	value	Effect
	(95% CI)		Size	(95% CI)		Size
	30 weeks			42 weeks		
Primary Outcomes						
CSS	-10.2 (-14.25, -10.2)	$F(1, 61.5) = 16.2$ $p < 0.001$	-1.52‡	-8.8 (-13.1, -4.6)	$F(1, 46.8) = 20.3$ $p < 0.001$	-1.31‡
WSAS	-6.6 (-10.4, -2.8)	$F(1, 50.3) = 11.2$ $p = 0.002$	-0.82‡	-6.6 (-10.3, -3.0)	$F(1, 46.9) = 9.8$ $p = 0.003$	-0.82‡
Secondary Outcomes						
CSS Informant	-3.94 (-9.1, -1.2)	$F(1, 50.2) = 2.4$ $p = 0.13$	-0.42‡	-3.6 (-8.6, 1.3)	$F(1, 40.1) = 4.4$ $p = 0.14$	-0.38‡

HADS Anxiety	-2.21 (-3.89, -0.52)	$F(1, 62.11) = 6.76$ $p = 0.012$	-0.60 [‡]	-2.3 (-3.9, -0.6)	$F(1, 45.6) = 6.4$ $p = 0.015$	-0.62 [‡]
HADS Depression	-2.04 (-3.46, -0.63)	$F(1, 64) = 8.24$ $p = 0.006$	-0.61 [‡]	-2.2 (-3.6, -0.8)	$F(1, 46.7) = 10.2$ $p = 0.002$	-0.66 [‡]
CORE-OM Total	-9.77 (-18.49, -1.03)	-	-0.52 [‡]	-9.8 (-18.3, -1.3)	-	-0.52 [‡]
CORE Problems	-4.7 (-8.71, -0.7)	$F(1, 56.4) = 5.48$ $p = 0.023$	-0.58 [‡]	-4.8 (-8.7, -0.9)	$F(1, 44.9) = 5.34$ $p = 0.025$	-0.59 [‡]
CORE Functioning	-2.33 (-6.01, 1.37)	$F(1, 60.9) = 1.59$ $p = 0.21$	-0.27 [‡]	-2.3 (-5.9, 1.3)	$F(1, 44.9) = 2.2$ $p = 0.28$	-0.27 [‡]
CORE Wellbeing	-2.25 (-3.95, -0.54)	$F(1, 66.16) = 6.86$ $p = 0.011$	-1.03 [‡]	-2.2 (-3.9, -0.6)	$F(1, 44.7) = 5.8$ $p = 0.020$	-1.01 [‡]
CORE Risk	-0.38 (-1.34, 0.57)	$F(1, 66.13) = 0.64$ $p = 0.43$	-0.18 [‡]	-0.3 (-1.2, 0.6)	$F(1, 44.4) = 0.54$ $p = 0.46$	-0.14 [‡]

CGI	Odds Ratio	Exact p test	Odds Ratio	Exact p test
	(95%CI)		(95%CI)	

CGI Improvement (Participant)	41.6 (4.9, 2005)	p < 0.001	-	23.1 (2.8, 1089)	p < 0.001	-
CGI Satisfaction (Participant)	35.0 (5.4, 429)	p < 0.001	-	23.2 (4.1, 190.2)	p < 0.001	-
CGI Improvement (Blind Assessor)	19.6 (2.4, 917)	p < 0.001		∞ (4.7, ∞)	-	

Abbreviations: CSS –Adult Barkley Current Symptoms Scale (Participant and Informant), WSAS – Work and Social Adjustment Scale, CGI – Clinical Global Impression Yes / No - (Participant Improvement and Satisfaction, Blind Assessor Improvement), HADS – Hospital Anxiety and Depression Subscale, CORE-OM - Clinical Outcomes in Routine Evaluation Outcome Measure.

† - Estimated group mean differences for treatment (CBT vs TAU) at 42 weeks are adjusted for baseline values of outcome, time-point of visit, interaction between treatment and time-point at 30 weeks and gender.

- Odds ratio for odds of improvement / satisfaction for CBT relative to TAU.

‡ - Standardized adjusted effect size is derived from the adjusted group mean difference divided by the baseline standard deviation of the measure.

Discussion

This is the first clinical trial to provide evidence for the effectiveness of formulation-driven CBT in adults with ADHD. As predicted, when added to TAU, CBT had significantly greater success in reducing both ADHD symptoms and improving occupational and social functioning than TAU alone and the sizes of these effects were large. At the main outcome point, mean scores on each of the primary outcomes for the CBT group had reduced to either below (CSS), or very close to (WSAS) the scale thresholds for clinical significance (11, 17).

CBT also provided statistically significantly greater improvements for most secondary outcomes including independently-rated CGI Improvement and self-rated anxiety, depression, global distress, CGI Improvement and CGI Satisfaction. Observer ratings of CSS were in the same direction as the self-report CSS, however this improvement was not statistically significant. Perhaps it takes more sustained improvement to change others' view of an adult with ADHD.

Our findings are encouraging as they suggest that formulation-driven CBT for adult ADHD is effective in reducing not only the core symptoms of the condition but also related impairment and emotional distress. All of our functional measures changed after CBT with the exception of the CORE Functioning subscale. However, it is also possible that the CORE Functioning subscale, which is a generic measure may not be the best measure of functioning and that participation in life specifically in relation to ADHD symptoms as assessed by the WSAS, our primary outcome, is more appropriate. It is therefore consistent with the NICE recommendations that adult ADHD treatments address functioning and emotional distress in addition to the core symptoms. Furthermore we had hypothesised that a benefit of the formulation-driven CBT approach was that it allowed concurrent treatment of the emotional impact of ADHD alongside the core symptoms themselves and results suggest this is indeed the case. This is of particular relevance given the high rates of co-morbid mood disorders in this patient group.

Equivalent use of medication between the two groups suggests the differences in outcomes are unlikely to be attributable to ADHD or other psychotropic medication. There were no important differences in safety outcomes between the treatments. Levels of adverse events were slightly higher in the CBT group. However it is possible that levels of reporting in this group were slightly higher since participants were asked about them at every CBT session, as opposed to just at the assessment points. Also, for the three CBT participants who had more than one event, events could have been related to each other (i.e. continuation of the original event).

There was a greater degree of engagement in the CBT condition evidenced by the lower loss to follow-up in this group. This is consistent with the participant satisfaction data where a significantly higher proportion of participants rated themselves as 'very satisfied' or 'moderately satisfied' compared with the TAU group. Therefore this study demonstrates that CBT is a highly acceptable treatment for patients.

The main outcome was 42 weeks post baseline. Results were similar at 30 weeks. Active CBT treatment took place up to 30 weeks and results therefore suggest that improvements were maintained at 12 weeks following the end of active treatment (see Figures 2 and 3).

Since this is a proof of concept trial, the effect sizes obtained are not definitive. However, they compare well with other adult ADHD CBT studies. RCTs of individualised CBT have found effect sizes on independently and self-rated ADHD symptom severity to be in the range of 1.2-1.7 when comparing individualised CBT with TAU and in the range 0.5-0.6 when comparing individualised CBT with relaxation and educational support (4, 5). Comparing effect sizes across ADHD treatment studies more widely, meta-analyses of methylphenidate (the NICE-guideline recommended first-line treatment for adult ADHD) compared with placebo have found average effect sizes range from 0.42

to 0.9 (22), however the differences in design should be taken into account (particularly active treatment comparison).

This study has several limitations. First, a high number of participants were lost to follow-up in the TAU group. However results of the sensitivity analysis suggest that even when taking this into account the treatment effect was robust.

Second the study design does not control for therapist time and attention and we are therefore unable to say whether the difference in results between the two treatment groups is due to the CBT as opposed to non-specific treatment effects.

Third, owing to resource constraints we were unable to follow up participants for longer to investigate whether CBT improved outcomes in the longer term. However the main outcome was at 42 weeks and active treatment ended at 30 weeks, so this study provides evidence that the effects do extend for at least 12 weeks beyond the end of active treatment.

Fourth there are some issues relating to generalisability of the findings. We excluded participants with an alternative primary diagnosis or severe co-morbidities utilising similar exclusion criteria to Safren et al's previous RCTs of individualised CBT for ADHD. We used the same exclusion criteria as the Safren studies because we wanted to include a similar sample and for the CBT to focus on ADHD and associated symptoms as opposed to a separate primary clinical problem. However, individualised formulations can be complex, taking account of several presenting diagnoses so it seems likely our formulation driven approach, which has been shown to be effective in reducing emotional distress, could be adapted for people with ADHD who have severe co-morbidities. The approach would likely incorporate features of protocols developed for relevant co-morbid conditions

while also addressing ADHD-related concerns. It is notable that while similar co-morbidity exclusion criteria were used in this study and the Safren studies, our screen-out rates were considerably different. We believe this is due to the differing referrals to the clinics – our referrals have highly variable presentations with many patients assessed either not receiving an ADHD diagnosis or having one or more co-morbidity from the study exclusion criteria.

Fifth we do not know whether different medication status has an effect on the outcomes. However the randomized controlled design controlled for any differences in medication between the two groups. It was unfortunately beyond the scope of the current study to investigate predictors or moderators of outcome such as medication.

Our CBT results also apply to people referred to specialist care. Therapists were highly trained and experienced and one therapist saw the majority of the cases. Investigation of the effectiveness of this intervention with a broader range of ADHD presentations (e.g. when it is not the primary problem) and in less specialist settings is now required. Blinding participants or clinicians to treatment allocation was not possible. The main outcomes were subjective and rated by participants. While this avoided investigator bias it could be subject to other biases. Expectations of treatment were not assessed at baseline so it is not possible to ascertain whether this had an effect. In this study ratings by the independent assessor who was blind to treatment allocation were also consistent with the self-rated measures. However, while a commonly used indicator of treatment effects, the accuracy of ADHD self-report has been found to be variable across studies (23, 24).

This study provides data which can be used to estimate the parameters needed to design a future larger trial of formulation-driven CBT for adult ADHD. We have used appropriate outcome

measures, defined a priori, which have been sensitive to changes following the interventions. We have established the willingness of participants to be consented and of clinicians to recruit participants. This study has also provided important information as to the number of eligible patients in specialist services and numbers lost to follow-up. Current data suggests future studies should aim to broaden the eligibility criteria to increase recruitment rates and generalizability of the findings. The current study suggests loss to follow-up may be more likely in treatment conditions involving less contact with a clinician.

Findings from this trial suggest that individually delivered formulation-based CBT when added to TAU is more effective than TAU alone in improving core symptoms, functioning and emotional distress and that this treatment is highly acceptable to patients. Future studies should assess the effectiveness of the intervention in a larger sample, with a broader range of patients and therapists as well as the use of a comparator therapy to control for therapist time and attention.

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Declaration of interest

None

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